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An assessment of annual procedure volumes and therapy adoption of transcatheter closure of patent foramen ovale in four European countries

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Abstract

Introduction: Patent foramen ovale closure reduces recurrence of cryptogenic ischaemic stroke compared to anti-platelet therapy. Our goal was to determine procedure volumes and closure utilisation as a proportion of candidates in four large European countries.

Patients and methods: National statistics were obtained for Germany, England, France, and Italy for the last available five years (2014–2018). Eligibility was aligned to the enrolment criteria of pivotal trials and current consensus documents. Stroke and transient ischaemic attack incidences were obtained from epidemiological registries and claims data. The eligible candidate pool for analysis included current year candidates plus untreated patients from the prior two years. Absolute strokes avoided assumed the hazard ratio for ischaemic stroke recurrence from a recent meta-analysis.

Results: In 2018, closure incidence rates were 5.64, 0.53, 2.94 and 5.26 per 100,000 in Germany, England, France and Italy, respectively. This reflects five-year increases of 128% in Germany, 462% in France and 36% in Italy ($p < 0.05$ for all), and a decline of 37% in England. The proportions of treated patients versus candidates for the combined stroke and transient ischaemic attack pool were 55%, 30%, 80%, and 6%, respectively.

Discussion: Patent foramen ovale closure volumes increased after the 2017 announcement of positive trial results but still differ substantially across large European countries. If all closure candidates in 2018 with prior ischaemic stroke were treated, the resulting absolute reduction of recurrent ischaemic strokes, compared to anti-platelet therapy alone, would be between 782 and 2295 across the four countries over five years.

Conclusion: Many eligible patients at risk for a recurrent cryptogenic event might remain untreated due to regional practice variations.

Keywords

Ischaemic stroke, foramen ovale, Patent, cryptogenic stroke, patent foramen ovale closure, Equipment and Supplies Utilization, Procedures and Techniques Utilization, underutilization, Health Services Misuse

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Introduction

Patent foramen ovale (PFO) is a common embryological remnant in the atrial septum of the heart which is associated with an increased risk of ischaemic stroke.[1] There is consensus that patients experiencing ischaemic stroke or transient ischaemic attack (TIA) of otherwise undetermined aetiology, with embolic appearances on imaging – commonly referred to as cryptogenic or paradoxical embolic events – should be evaluated for presence of a PFO. Transcatheter closure of PFOs using catheter-based systems has been available as a therapeutic option since the early 1990s. However, uncertainty remained regarding efficacy of stroke prevention until recently.[2] Despite the absence of clinical evidence in the form of positive randomised controlled trials (RCTs), closure adoption spread across Europe in the early 2000s.[3] With three RCTs published in 2012–2013 unable to demonstrate a statistically significant reduction in the composite primary outcome of all-cause mortality or recurrent stroke/TIA, there continued to be an absence of definitive evidence about the value of the therapy in terms of stroke prevention.[4–6] This changed with the publication of several RCTs in 2017–2018[7–10] whose results supported the conclusion that closure in selected patients with cryptogenic stroke presumed to be from a PFO is superior to medical therapy in terms of preventing subsequent ischaemic stroke.[2,11,12]

In light of this new evidence, our objectives were to study the adoption patterns of closure in four large European countries and to estimate the current adoption relative to a calculated theoretical candidate pool.

Methods

We obtained national statistics for Germany, England, France, and Italy for up to ten years through the latest data year, 2018. Procedural volumes and age distributions were analysed, and treatments in patients younger than 60 years compared to a theoretical candidate pool for this age group, calculated based on country-specific ischaemic stroke and TIA incidence and on proportions of the presence of eligibility criteria.

Procedure Volumes

Procedure volumes for all countries were obtained from national databases for years 2012–2018. Where available, earlier data years up to 2008 were also collected. For England, data were obtained from Hospital Episode Statistics (HES) data for the closure-specific procedure code K16.5 (OPCS Classification and Intervention Procedures Version 8.4). As HES data use a time period starting mid-year, we considered the mid-2018 through mid-2019 period as the 2018 value for England and applied the same procedure backwards. For France, data were obtained from the French National Uniform Hospital Discharge Data Set Database (PMSI-MCO, via Agence Technique de l'Information sur l'Hospitalisation, ATIH) for the closure-specific procedure code DASF005 ('Fermeture d'un foramen ovale perméable, par voie veineuse transcutanée'). For Germany, annual procedure volumes were obtained from the Diagnosis-related group (DRG) Statistics (German Federal Statistics Office, Destatis). Closure procedures are coded using procedure code 8-837.d0. As this code is a code that also captures transcatheter atrial septum defect (ASD) closure procedures, we estimated the proportion of PFO closure volume as follows: first, we assumed that none of the procedures in patients under 20 years of age are PFO closure procedures, and second, that age distributions for ASD and PFO closure procedures reported for England are reasonably representative for Germany to calculate a volume adjustment factor. This adjustment factor of 0.76 (see Supplementary Materials for detail) was subsequently applied to obtain the closure volumes for Germany. For Italy, closure procedure volumes were obtained from the national registry of the Italian Interventional Cardiology Society (GISE – Società Italiana di Cardiologia Interventistica, Milan, Italy). In addition to total volumes, data for specific age groups, reported in five-year increments, were available for all countries except Italy.

Stroke and TIA Incidence

To estimate country-specific theoretical candidate pools for closure, stroke and TIA incidences were determined as follows. The country-specific incidences of ischaemic stroke for France, Germany and Italy were computed from the total population size and country-specific stroke rates identified in a recent pan-European review summarising epidemiological evidence from stroke incidence studies.[13] These age-standardised rates, based on the Dijon (France), Ludwigshafen (Germany), and Puglia (Italy) stroke incidence studies, which were epidemiological registries,[14–16] rates were then multiplied by the study-specific proportion of non-haemorrhagic stroke to obtain ischaemic stroke incidence rates. The resulting annual rates for France, Germany and Italy were 85, 123 and 113 per 100,000, respectively. For England, age-standardised stroke incidence was based on data reported for 2016 by Public Health England, yielding an estimate of 88 per 100,000 based on an assumed ischaemic stroke proportion of 78%.[13]

We also identified the volumes of hospitalised patients for whom ischaemic stroke was listed as primary diagnosis, to compare with the epidemiology-based estimates.

For TIA incidence, we assumed the same age-standardised TIA rate of 29 per 100,000 for all countries, based on a recent study conducted by Degan et al. in the Italian setting.[17]

Calculation of the Theoretical Closure Candidate Pool

The theoretical closure candidate pool was calculated using the following approach: First, based on studies using a complete contemporary cryptogenic stroke workup, we estimate that 45% of all ischaemic strokes and 50% of TIAs were cryptogenic.[18,19] The effect of variation in the cryptogenic stroke proportion was explored in sensitivity analyses. Second, based on recent data from the OXVASC study, we assumed that a PFO was present in 37% of these cryptogenic stroke events.[20] Third, in line with inclusion criteria from the recent RCTs[7–10] and a European consensus statement,[11] we used an upper bound of 60 years of age for inclusion. Based on the age distribution of ischaemic stroke admissions in Germany and the UK, we estimated that 15% of strokes occur in patients 60 years or younger. Fourth, we used recently reported in-hospital mortality of 5.2% for ischaemic stroke patients from a prospective German database.[21] Fifth, based on data from a large stroke registry, we assumed 95% of survivors 60 years or younger have a modified Rankin scale (mRS) score of 3 or lower and can therefore be considered as closure candidates.[22] For the TIA cohort, we assumed no disease-specific mortality. Together, this yielded a total annual estimate of closure candidates of 2.2% of ischaemic stroke patients, and 2.8% of TIA patients.

To calculate a theoretical closure candidate pool, we added to this annual estimate the number of candidates in the previous two years who did not undergo closure (i.e., for each year, we calculated the difference between annual volume, per above, and the reported closure treatment volume in the respective prior year).

Avoidable Strokes

The absolute number of avoidable strokes was calculated using the hazard ratio for ischaemic stroke recurrence of 0.32 reported in a recent meta-analysis.[2] The recurrent annual stroke rate was assumed to be 2.2% from the control arm of the REDUCE study.[7] We converted this proportion via rates to a five-year horizon and calculated the number of avoidable strokes for this follow-up horizon. Based on the 2018 closure candidate pool of stroke patients only, the potential number of recurrent strokes that could be avoided in each of the four countries in the patient group 60 years or younger was calculated.

Statistical Analysis

Treatment age, where reported, was analysed by plotting the age-bracket specific proportion of treatments as part of the total and comparing the resulting distributions across countries.

Closure procedure incidence per 100,000 population was analysed for each country for the period 2014–2018, using country-specific population data as reported for each year by EuroStat.

Further, the proportion of 2018 treatment volume relative to the calculated closure candidate pool in that year was determined. For each of the four countries, we analysed the absolute and relative change in procedure volumes during the five-year period 2014–2018, and calculated p values for trend using Cuzick's method.[23] All statistical testing was performed using STATA IC15 (StataCorp, College Station, TX, U.S.A.).

Findings

Procedure volumes showed markedly different adoption in the four studied countries over the last decade. Volumes in Germany, England and Italy showed an absolute decline in the early 2010s, Figure 1. In France, early adoption was associated with low volumes, and no comparable decline was visible. For all countries except England, absolute volumes increased markedly since 2016. During the latest available data year (2018), closure was performed in 4668, 295, 1962, and 3192 cases in Germany, England, France, and Italy, respectively. This corresponded to procedure incidence rates of 5.64; 0.53; 2.94; and 5.26 per 100,000 population (Figure 1). These latest volumes result from a total five-year increase in procedure volumes of 128% in Germany; 462% in France; 36% in Italy; and from a decline by 37% in England. The largest absolute increases in Germany, France and Italy were observed between the 2017 and 2018 data years (an additional 2140; 1335; and 520 procedures, respectively). In all studied countries except England there was a statistically significant trend to higher procedure volumes over time ($p < 0.05$).

The distributions of treatment age were consistent between the 2014 and 2018 data years for England and Germany but showed a shift from higher treatment age toward lower treatment age in France (Figure 2). In 2018, around 87% of procedures in England were performed in patients younger than 60 years, compared to 75% in France and 67% in Germany. The proportions were 92.1%, 85.0% and 78.5%, respectively, for age less than 65 years, and 96.6%, 90.8% and 87.2% for age less than 70 years. The annual number of closure candidates younger than 60 years of age ranged from 1560 in France to 2954 in Germany (Table 1).

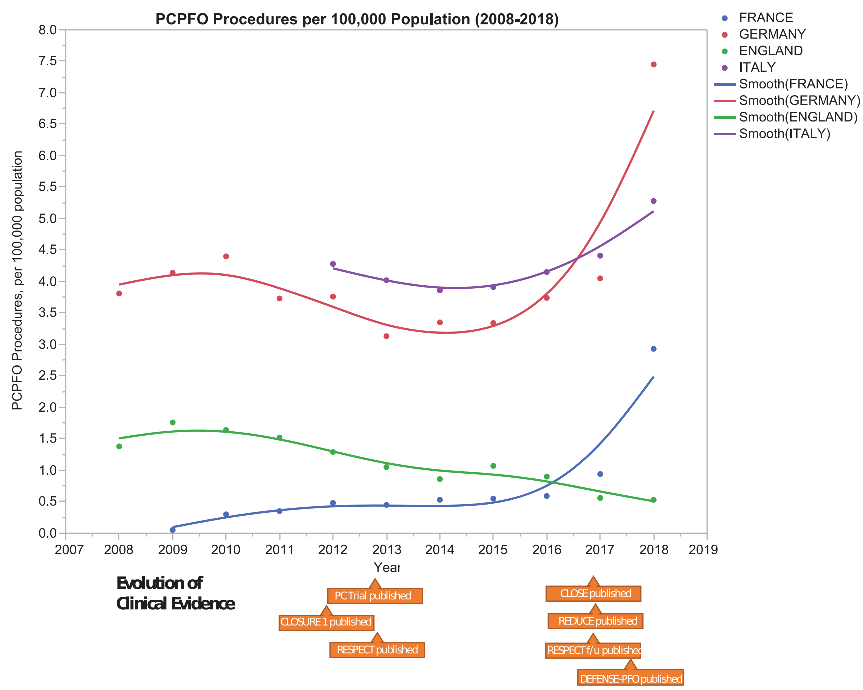

Figure 1. Patent foramen ovale closures per 100,000 population in the four studied countries for 2008 to 2018, and concurrent evolution of clinical evidence.

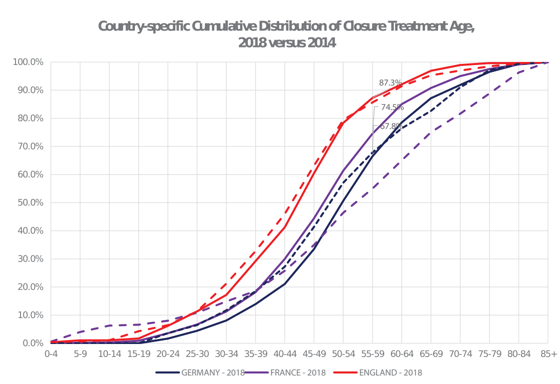

Figure 2. Country-specific cumulative distribution of transcatheter closure treatment age, years 2018 to 2014.

Applying these numbers to the 2018 candidate pool calculation, which takes into account the calculated annual stroke and TIA candidate volume (<60 years of age) for a three-year period (2016–2018) minus the reported closure treatments in 2016 and 2017, yielded an estimate of 3998 patients for England, of 4838 for France, of 5683 for Germany, and of 2639 for Italy. Procedures performed in 2018 in patients younger than 60 years of age, relative to this 2018 combined candidate pool, suggest a wide difference of current therapy utilisation in this patient group, ranging from 6% in England to an estimated 80% in Italy. When limiting the pool to ischaemic stroke only, the pool size estimates were 2640 for England, 3219 for France, 3679 for Germany, and 1524 for Italy. Using stroke incidence estimates based on country-specific administrative data as opposed to the epidemiological study data changed the pool size estimates to 9168 for England, 6499 for France, 14,267 for Germany, and 2551 for Italy. See Figure 3 for corresponding percentages of therapy utilisation, and Supplementary Materials for additional scenario analyses, including the effect of variation in the assumed proportion of cryptogenic stroke.

Based on a 2.2% annual proportion of ischaemic stroke recurrence reported in the REDUCE trial,[7] the number of recurrent stroke events over five years in the calculated 2018 closure candidate pool with prior ischaemic stroke event ranged from 158 in Italy to 382 in Germany when epidemiological stroke incidence data were considered, and from 265 to 1482 when administrative data were considered. Applying the meta-analysis-based hazard ratio of 0.32 with closure treatment, yielded numbers of theoretically avoidable recurrent stroke events between 108 in Italy and 260 in Germany based on epidemiological stroke data and 180 and 1008 based on administrative stroke data, assuming each subject in the candidate pool would be treated and followed over five years (see Table 2).

Table 1. Calculation of annual number of percutaneous patent foramen ovale closure candidates younger than 60 years of age.

Parameter	England	France	Germany	Italy	Sources
Population in 2018	56,075,912	66,926,166	82,792,351	60,483,973	Eurostat, UK Office for National Statistics
Incidence of ischaemic stroke, per 100,000	88.1	85.3	123.3	112.5	Calculated based on literature[13,15,16,35]
Resulting estimated number of ischaemic strokes annually	*49,425*	*57,061*	*102,042*	*68,044*	*Calculated from above*
Proportion cryptogenic		45%			[19]
PFO present in cryptogenic event population		37%			[20]
Proportion of stroke patients under the age of 60		15%			Estimate based on administrative data of ischaemic stroke
Proportion surviving in-hospital admission for stroke		95%			[21]
Proportion of survivors with mRS 3 or lower		95%			Estimate for population <60 years of age[22]
Resulting estimated number of closure candidates from cryptogenic stroke	*1107*	*1278*	*2286*	*1524*	*Calculated from above*
Corresponding percent of closure candidates relative to total ischaemic stroke volume		*2.2%*			*Calculated from above*
Incidence of TIA, per 100,000		29.00			[17]
Resulting estimated number of TIA events	*16,262*	*19,409*	*24,010*	*17,540*	*Calculated from above*
Proportion cryptogenic		50%			[20]
PFO present in cryptogenic event population		37%			
Percent of TIA events in patients under the age of 60		15%			Assumed same as for stroke, per above
Percent surviving TIA event		100%			Assumption
Resulting estimated number of closure candidates from cryptogenic TIA	*452*	*535*	*662*	*483*	*Calculated from above*
Corresponding percent of closure candidates relative to total TIA volume		*2.8%*			*Calculated from above*
Total annual number of closure candidates younger than 60 years of age	*1560*	*1818*	*2954*	*2012*	*Sum of closure candidates from stroke and TIA*

PFO: patent foramen ovale; TIA: transient ischaemic attack; mRS: modified Rankin Score; UK: United Kingdom.

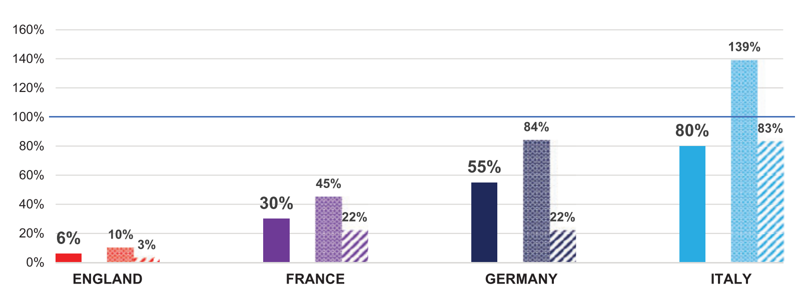

Figure 3. 2018 percutaneous patent foramen ovale closure procedure volumes in patients younger than 60 years of age, relative to calculated percutaneous patent foramen ovale closure candidate pool of patients younger than 60 years of age. Left column: combined stroke and TIA candidate pool; centre column: stroke candidate pool only (based on epidemiological stroke incidence data); right column: stroke candidate pool only (based on administrative stroke incidence data). Note: In the absence of Italian age data, the respective estimate assumes an age distribution for percutaneous patent foramen ovale closures similar to Germany.

Table 2. Projected number of recurrent stroke events over a five-year follow-up time horizon for a calculated 2018 patent foramen ovale closure candidate pool of patients with prior ischaemic stroke, no closure versus closure treatment, and resulting numbers needed to treat.

	All prior ischaemic stroke candidates treated without PFO closure	All prior ischaemic stroke candidates treated with PFO closure	Absolute risk difference	Number needed to treat
	Estimated number of recurrent stroke events over five years, based on *epidemiological* stroke incidence data			
England	415	133	282	14
France	503	161	342	
Germany	590	189	401	
Italy	274	88	186	
	Estimated number of recurrent stroke events over five years, based on *administrative* stroke incidence data			
England	953	305	648	14
France	675	216	459	
Germany	1482	474	1008	
Italy	265	85	180	

PFO: patent foramen ovale.
Top: based on epidemiological stroke incidence data; bottom: based on administrative stroke incidence data.

Discussion

Our study provides information about current adoption and utilisation patterns of closure in four important European healthcare systems. The results show substantial variation in treatment volumes, with Germany and Italy exhibiting treatment volumes that are more than 10 times higher than those observed in England. Except for England, with its centralised National Health Service which did not reach a clear PFO commissioning position until late 2019, our data show significant growth trends in the period 2014–2018, with most pronounced growth after publication of the positive RCT data from REDUCE, RESPECT and CLOSE.[7–9] Further, our data suggest between 13% and 33% of treated patients are older than the trial inclusion criteria. Patterns of treatment by age do not seem to have changed in the German and English healthcare systems between the 2014 and 2018 data years but suggest a downward shift in France toward treatment ages that are more closely aligned with the German and English data. Relative to the calculated combined candidate pool of stroke and TIA patients 60 years or younger, 2018 treatment volumes suggest Germany and Italy are approaching the theoretical size of the candidate pool, while French volumes reached only one-third and England only one-twentieth of patients expected to benefit from closure. Limiting the candidate pool to prior ischaemic stroke patients elevated the utilisation percentages, with Italy's 2018 treatment volume exceeding the calculated pool. However, when performing the analysis based on stroke incidence rates from country-specific administrative data as opposed to epidemiological studies, utilisation percentages were substantially lower (Figure 3).

The results presented here may provide useful guidance to stakeholders such as physicians, health care administrators and policy makers who all may consider individual pieces of evidence, treatment guidelines, therapy adoption and reimbursement matters for their decisions. Our findings complement the recent clinical literature,[2,24–26] including a meta-analysis reporting on closure for the prevention of recurrent stroke,[2] as well as some economic evaluations comparing closure to medical management.[27–29] These cost-effectiveness analyses, conducted for the UK and US settings, suggested that the additional cost for closure treatment may be well spent given the improved patient outcomes and associated downstream reductions in healthcare costs and freedom from disability associated with stroke.

An important topic for future discussion and research is the eligibility of patients older than 60 years of age, a cut-off we adopted for our candidate pool calculations in line with the inclusion criteria of most RCTs and current consensus statements.[11,12] Our findings demonstrate the proportion of patients treated older than 60 years of age is not insignificant in all studied healthcare systems, accounting for up to a third of reported activity in Germany. Findings from a recent population-based study nested in OXVASC suggest that more than half of identified patients with large right-left shunt and cryptogenic TIA or non-disabling stroke might occur in patients older than 60 years.[20] Based on such findings, these authors advocated for an RCT in this older population to explore a potential benefit in this subgroup. If this is indeed confirmed, the country-specific candidate pools might be substantially larger than our current estimates.

Part of the differences in therapy adoption may be related to therapy reimbursement. PFO occluders are reimbursed under DRG in Germany. Italy established an add on-payment for the implantable device similarly to England and France where occluders are listed in a generic line with add-on payment on top of the DRG tariff that covers the procedural and hospital costs. While reimbursement existed without limitation in Germany over the analysis horizon, volume limits did exist in several of the other studied countries (see Supplementary Materials for detail). It is safe to assume that the observed adoption volumes in England were heavily influenced by payer decisions about volume and reimbursement. Further, adoption of new interventions might follow different patterns between countries depending on evidence requirements for reimbursement, and general preference or skepticism about rapid uptake of novel interventions.

Among the strengths of the current analysis is the detailed analysis of contemporary real-world data on therapy adoption, and its side-by-side comparison of closure utilisation in four different European healthcare systems. In addition, we provide estimation of therapy adoption relative to our calculated closure candidate pool, which to our knowledge has previously not been done, but may provide useful guidance for those wishing to reduce stroke recurrence in young populations.

However, our analysis is subject to several limitations. First, volume data are derived from administrative records (England, France, Germany) or societal registries (Italy). The accuracy of these data depends on the correct coding for the closure procedures at time of treatment. Further, these data sources do not provide information about the specific indications for the performed closure procedures. Second, while closure-specific codes exist in England, France and Italy, the German procedure code captures all atrial septal defect closures. While we corrected for this by an adjustment factor, there is still some uncertainty about the true PFO closure volumes. Third, our estimation of annual closure candidates – and by extension – of the 2018 theoretical closure candidate pool, hinges on the accuracy of several assumptions. While the numbers of ischaemic stroke events for our base case calculation were estimated based on country-specific registry information collected in the 2000s, there still remains uncertainty about the true representativeness of these regionally collected numbers for the respective country at large. Specifically, registry-based approach estimates for annual ischaemic stroke volumes are sometimes less than half the in-patient treatments coded with ischaemic stroke as the primary diagnosis. The same holds for TIA incidence, for which we used the most recent study data,[17] which reported lower TIA incidence than previous studies, including OXVASC.[30] Further, the assumptions on the proportion of cryptogenic events with a PFO present arise from the scenario reflecting contemporary evidence for the respective parameters. Yet prior studies show variation in these, ranging from less than 30% to higher than 60%, with directionally higher percentages in younger patients such as those considered in our analysis.[20,31–33] In consequence, the calculated candidate pool could be somewhat smaller or larger than our estimate, as we documented in our analyses shown in the Supplementary Materials. The same holds true for the assumptions regarding percentage of stroke and TIA patients below age 60 estimated from administrative English and German data on ischaemic stroke incidence which may differ from incidence of cryptogenic stroke; and also for the assumed survival of ischaemic stroke events based on contemporary in-hospital data from Germany compatible with other recent reports,[34] but for a population that is likely older. Collectively, these limitations produce a point estimate of a candidate pool that, while reasonable and credible, is subject to systemic uncertainty. However, our overall objective to approximate the potential candidate pool (rather than provide a definitive absolute number) was met, and in that regard the four European healthcare systems studied produce a range of population level estimates that are perhaps of more value than a single analysis of a single country.

Conclusion

With an apparent increase in PFO closure following the 2017 announcement of pivotal trial results, historical procedure volumes suggest that a sizeable legacy cohort of patients who may derive benefit from closure exists in Europe. This patient population will be greatest in jurisdictions with the lowest procedural volumes.

Declaration of conflicting interests

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Guarantor

JBP.

Contributorship

JBP, BPG, RMB, LS and SEK conceived the presented idea. JBP, BPG and RMB developed the model and performed the computations. MJD and GT contributed data. JBP and BPG wrote the initial draft of the manuscript. MJD, RMB, GS, LS and SEK critically revised the manuscript. JBP, LS and SEK supervised the project.

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Supplemental Materials

Supplemental materials for this article are available online.

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